REMARKS

Reconsideration is respectfully requested.

The Specification has been amended at pages 37 and 38 to include SEQ ID NOs for disclosed sequences. No NEW MATTER has been entered.

Claims 1-12, 14-25, 28-31, and 37-38 have been cancelled. Original claims 32-34, 36, and 40 have been reiterated. Claims 13, 26, 27, and 39 have been amended. Claims 41-62 have been added. Support for claim 41 may be found, for example, at page 37, Table 5. Claim 42-62 which depend from the method of claims 35 and 36, are each directed to specific sequences in claims 35 and 36.

After entry of the present amendment, claims 13, 26-27, 32-36, and 39-62 will be pending.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Restriction Requirement

Applicants acknowledge the finality of the restriction requirement. Applicants note the Examiner's comment that "the restriction requirement between linked inventions is subject to the nonallowance of the linking claim(s), claims 32-34." Applicants respectfully assert, as detailed below, that claims 32-34 are allowable. As such, the restriction requirement should be withdrawn for those claims dependent thereon.

Objections to the Disclosure

The Examiner has objected to the Disclosure for two informalities.

A. "Ogligonucleotides"

Applicants have amended claim 26 to read "oligonucleotides."

This amendment only makes explicit what was already implicit in the claims. The amendment merely corrects a typographical error, and is unrelated to patentability.

Applicants respectfully request that this ground for objection be withdrawn.

B. SEQ ID NOs

The Examiner has objected to the Specification because the SEQ ID NOs have not been used to identify each sequence listed as required by 37 CFR §1.821(d). The Examiner points to pages 37 and 38 of the specification.

Applicants have amended the Specification to include SEQ ID NOs on pages 37 and 38, as required by the Examiner.

Applicants respectfully request that this ground for objection be withdrawn.

I. Rejections under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claim 26 under 35 U.S.C §112, second paragraph.

Claim 26

Claim 26 recites "an oligonucleotide probe comprising the formula

$$[X\text{-}Y\text{-}Z]_n$$

wherein X is a sequence of 0 to 100 nucleotides or nucleotide analogs;
Y is an oligonucleotide consisting of SEQ ID NO:15, and
Z is a sequence of 0 to 100 nucleotides or nucleotide analogs, and
N is 1-500."

The Examiner's Rejection

The Examiner has rejected claim 26 as indefinite under 35 U.S.C. §112, second paragraph for allegedly failing to particularly point out and distinctly claim the subject matter Applicant regards as the invention. First, the Examiner alleges that "it is unclear as to how claim 26 is intended to be further limiting from claim 13." Second, the Examiner alleges that "it is unclear as to whether Y is to be one or more of the oligonucleotides listed in claim 13 (i.e. Y = one or more copies of SEQ ID NO:15) or whether Y is one or more copies of any oligonucleotide."

Applicant's Response

The Examiner appears to reject claim 26 for two reasons: first, that it is unclear how claim 26 further limits claim 13, and second that it is unclear as to whether Y is the oligonucleotide of claim 13.

Claim 26 has been amended to be independent, and no longer depends from claim 13. Further, claim 26 now includes the limitation "consisting of SEQ ID NO:15."

Therefore, this rejection is now moot. Applicants respectfully request that it be withdrawn.

Rejections under 35 U.S.C. §102(b)

A. Rejection under 35 U.S.C. §102(b) over Lee (GenBank Accession No. AF042820)

The Examiner has rejected claims 13, 16, and 26-28 over Lee.

Claims 13, 16, and 26-28

Claim 13 is directed to "an isolated oligonucleotide consisting of the nucleotide sequence of SEQ ID NO: 15."

Claim 16 has been cancelled.

Claim 26 is directed to "an oligonucleotide probe comprising the formula

$$[X\text{-}Y\text{-}Z]_n$$

wherein X is a sequence of 0 to 100 nucleotides or nucleotide analogs;

Y is an oligonucleotide consisting of SEQ ID NO:15, and

Z is a sequence of 0 to 100 nucleotides or nucleotide analogs, and

N is 1-500."

Claim 27 is directed to "pair of oligonucleotides wherein the first oligonucleotide has the nucleotide sequence of SEQ ID NO: 15 and the second oligonucleotide has the sequence of SEQ ID NO: 8."

Claim 28 has been cancelled.

The Examiner's Rejection

With respect to claims 13, 16, and 26, the Examiner alleges that "claims 13, 16, and 26 are drawn to oligonucleotides comprising SEQ ID NO: 15." The Examiner states that the

sequence cited by Lee "teaches nucleic acids comprising the 24S large subunit ribosomal RNA sequence of *Heterosigma akashiwo*." (Emphasis added). Further, the Examiner admits that only "the complementary inverse strand of this rRNA contains the 22mer nucleotide sequences of SEQ ID NO:15." (Emphasis added).

With respect to claims 27 and 28, the Examiner again admits that only "the inverse complementary strand of the rRNA of Lee also contains the nucleotide sequence of the 22-mer of SEQ ID NO:8."

The Cited Reference

The reference discloses a single 24S ribosomal RNA fragment.

The Cited Reference Distinguished

In order to anticipate under 35 U.S.C. §102, every element of the claimed invention must be identically shown in a single reference. *In re Bond,* 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

a. Claim 13

Applicants respectfully traverse the Examiner's rejection of claim 13. Without acquiescing or admitting to the rejection, claim 13 has been amended to recite "an isolated nucleotide consisting of the nucleotide sequence of SEQ ID NO:15." (Emphasis added.) Lee discloses a sequences including the inverse complement of SEQ ID NO:15 and flanking sequences, but fails to teach the specific sequence consisting of SEQ ID NO:15.

In view of the amendment, the Examiner's rejection is therefore moot. Applicants respectfully request that it be withdrawn.

b. Claim 26

Lee fails to teach all limitations of claim 26.

Lee fails to include the additional limitations directed to nucleotide or nucleotide analogs X, Z, and N, and do not teach a probe having the repeating structure of formula $[X\text{-}Y\text{-}Z]_n$. Lee does not teach or suggest a component X that "is a sequence of 1 and 100 nucleotide analogs." Further, Lee fails to teach or suggest a component Z that "is sequence of 1 to 100 nucleotides and nucleotide analogs." While Lee teaches a sequence comprising the inverse complement of SEQ ID NO:15, the reference fails to teach the range limits required for X and Z. Accordingly, Lee fails to anticipate claim 26.

Since Lee et al. fail to teach every limitation of claim 26, Applicants respectfully request that this ground for rejection be withdrawn.

c. Claim 27

Lee fails to teach all limitations of claim 27. Claim 27 is directed to "a pair of oligonucleotides." (Emphasis added). Lee fails to disclose, mention, or hint at "a pair of oligonucleotides." The application discloses pairs of non-covalently linked oligonucleotides in a sandwich assay (see, for example, page 16, line 23 – page 17, line 26). By contrast, Lee teaches only a single oligonucleotide that is complementary to either SEQ ID NO:15 or SEQ ID NO:8. A single oligonucleotide is not a pair of oligonuleotides. Therefore, Lee fails to anticipate claim 27.

Since Lee et al. fail to teach every limitation of claim 27, Lee fails to anticipate the claims. Applicants respectfully request that this ground for rejection be withdrawn.

B. Rejection under 35 U.S.C. §102(b) over Asai (Nippon Kagakkai Koen Yokoshu 1998, Vol. 75 page 315)

The Examiner has rejected claim 32 over Asai.

Claim 32

Claim 32 recites "a method of detecting a raphidophyte cell, comprising: a) permeabilizing said cell to expose the ribosomal RNA of said cell wherein said RNA has hypervariable regions; b) contacting the exposed RNA under hybridizing conditions with oligonucleotide probes capable of selectively hybridizing to said hypervariable regions to form a hybridization complex and c) identifying said hybridization complex to detect said raphidophyte cell."

The Examiner's Rejection

The Examiner alleges that "Asai teaches a method for detecting the raphidophyte *Heterosigma akaskhiwo*." The Examiner asserts that in "Asai, the nucleotides of *H. akashiwo* are released from the cell." The Examiner assumes that this step "is considered to be a step of permeabilizing a cell to expose ribosomal RNA." In addition, the Examiner states that "the 18S rRNA sequences are hybridized with oligonucleotide primers and amplified by PCR." The Examiner assumes that this step "is considered to be a step of contacting RNA with a probe capable of hybridizing to a hypervariable region." The Examiner further asserts that "the

amplified PCR products are detected as indicative of the presence of a raphidophyte cell." The Examiner assumes that this step "is considered to be a step of identifying hybridization complexes." Finally, the Examiner alleges that "Asai teaches that this method is useful for monitoring samples for the presence of the red tide phytoplankton *H. akashiwo* since this organism is associated with fish death."

The Cited Reference

Asai is a meeting abstract that teaches applying "fluorescence polarization ...to monitoring ...red tide phytoplankton, Heterosigma akashiwo, which frequently caused fish death." The reference discloses that "first, 18S ribosomal RNA of dominant phytoplankton causing red tide was analyzed and a pair of the 20mer oligonucleotide was found as specific primers. The PCR was performed to amplify an entire rRNA sequence and its PCR product was observed by electrophoresis. Then, the PCR product of the FITC-labeled primer was applied to fluorescence polarization measurement. The increase of fluorescent polarization intensity of its PCR product was observed."

The Cited Reference Distinguished

In order to anticipate under 35 U.S.C. §102, every element of the claimed invention must be identically shown in a single reference. *In re Bond,* 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990). Asai fails to anticipate the claims, since the reference fails to teach multiple elements of the claims.

First, Asai fails to disclose, mention, or hint at RNA having "hypervariable regions," or "contacting ...RNA under hybridization conditions with oligonucleotide probes capable of selectively hybridizing to a hypervariable region." (Emphasis added). Claim 32 thus requires that the hybridization probes used to contact the RNA are capable of selectively hybridizing to a hypervariable region. Asai, however, only teaches primers that amplify 18S RNA. Asai provides no indication that the primers hybridize to hypervariable regions. Since Asai fails to even hint at hypervariable regions, the reference fails to anticipate the claims.

Second, Asai does not teach "identifying said hybridization complex to detect said raphidophyte cell." Asai teaches amplifying 18S RNA using FITC labeled primers, and applying a fluorescent polarization measurement to the resulting amplified product. Instead, Asai teaches detecting the fluorescence polarization intensity of an amplified PCR product. Thus, Asai does

not teach identifying the "hybridization complex" made by the primer and the 18S RNA. Since Asai does not teach identifying a "hybridization complex," Asai fails to meet every limitation of the claimed invention.

Asai therefore fails to make the vaguest reference to hypervariable regions or probes capable of selectively hybridizing to hypervariable regions. Asai also fails to disclose detecting a "hybridization complex." Therefore, Asai fails to anticipate claim 32.

Applicants respectfully request that this ground for rejection be withdrawn.

Rejection under 35 U.S.C. §103(a)

The Examiner has rejected claims 32-34, 36, 39, and 40 under 35 U.S.C. §103(a) over Asai in view of Scholin (reference 22) and Lee.

35 U.S.C. § 103(a) requires that "...differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). The prima facie case must satisfy three requirements: 1) the references must teach or suggest all the claim limitations; 2) the prior art combined with general knowledge must include a suggestion or incentive to modify or combine the references; and 3) the modification or combination must have a reasonable chance of success.

Claims 32-34, 36, 39, and 40

Claim 32 recites "a method of detecting a raphidophyte cell, comprising: a) permeabilizing said cell to expose the ribosomal RNA of said cell wherein said RNA has hypervariable regions; b) contacting the exposed RNA under hybridizing conditions with oligonucleotide probes capable of selectively hybridizing to said hypervariable regions to form a hybridization complex and c) identifying said hybridization complex to detect said raphidophyte cell."

Claim 33 recites "the method of claim 32 wherein said hybridization complex is identified in a sandwich hybridization assay."

Claim 34 recites "the method of claim 32 wherein said hybridization complex is identified in a fluorescent in situ hybridization assay."

Claim 36 recites "the method of claim 32 wherein said oligonucleotide probes have sequences selected from the group consisting of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22 and SEQ ID NO:23."

Claim 39 recites "an oligonucleotide kit for detection of raphidophyte cells comprising an oligonucleotide consisting of the nucleotide sequence of SEQ ID NO: 15."

Claim 40 recites "the kit of claim 39 further including one or more hybridization buffers."

The Cited References

Asai is a meeting abstract that teaches applying "fluorescence polarization ...to monitoring ...red tide phytoplankton, Heterosigma akashiwo, which frequently caused fish death." The reference discloses that "first, 18S ribosomal RNA of dominant phytoplankton causing red tide was analyzed and a pair of the 20mer oligonucleotide was found as specific primers. The PCR was performed to amplify the entire rRNA sequence and its PCR product was observed by electrophoresis. Then, the PCR product of the FITC-labeled primer was applied to fluorescence polarization measurement. The increase of fluorescent polarization intensity of its PCR product was observed."

Lee teaches a 24S ribosomal RNA fragment of which only the inverse complement is the same sequence. 24S ribosomal RNA is not double stranded. The reference only discloses a fragment of 24S ribosomal RNA.

Scholin et al. disclose large-subunit ribosomal RNA (LSU rRNA) targeted oligonucleotides specific to *Pseudo-nitzschia australis*, a species of algae. The reference describes methods of assaying for rRNA in whole cell and sandwich assays. Scholin et al fail to disclose raphidophytes or raphidophyte rRNA. Further, Scholin et al. also fail to disclose "hypervariable" regions in raphidophytes, and instead teaches variable differences between algal species.

The Examiner's Rejection

The Examiner alleges that "Asai teaches a method for detecting the raphidophyte *Heterosigma akaskhiwo*." The Examiner asserts that in "Asai, the nucleotides of *H. akashiwo* are released from the cell, the 18S rRNA sequences are hybridized with oligonucleotide primers and amplified by PCR and the amplified PCR products are detected as indicative of the presence of a raphidophyte cell." The Examiner alleges that "Asai teaches that this method is useful for monitoring samples for the presence of the red tide phytoplankton *H. akashiwo* since this organism is associated with fish death."

The Examiner further alleges that "Scholin teaches methods for detecting microalgal species in environmental samples." The Examiner states that the reference "teaches that microorganisms can be detected using either a fluorescent *in situ* hybridization method or sandwich hybridization method (pages 192-193)." The Examiner also asserts that Scholin teaches that sandwich hybridization provides many advantages including ease of detecting a microoganism and adapability to fluorescence activated cell sorting. In addition, the Examiner asserts that, according to Scholin et al., "methods for identifying LSU rRNA prove useful for performing the detection methods" and that "LSU rRNA is useful as a probe because it contains hypervariable sequences and because rRNA is present in the cell at a high copy number." Finally, the Examiner asserts that Scholin teaches the reagents necessary to perform the disclosed hybridization method."

The Examiner argues that "in view of the teachings of Scholin and Lee, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Asai so as to have detected *H. akashiwo* using the sandwich hybridization or fluorescent *in situ* hybridization assay of Scholin in order to have provided an equally effective means for detecting *H. akashiwo* and to have provided sandwich hybridization methods which could be performed rapidly and in an automated format and to have provided fluorescent *in situ* hybridization methods which could be used to identify and isolate the positivley labeled *H. akashiwo* cells."

The Examiner further alleges that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the 24 S rRNA sequences of Lee

comprising the 22 mer of SEQ ID NO:15 as a probe since Scholin teaches that the LSU rRNA provides a useful probe for detecting microorganisms. The Examiner also states that "the specification (page 36) teaches the improved results obtained when using probes consisting of SEQ ID NO:15," but then alleges that "the claims are broadly drawn to probes and methods of using probes comprising SEQ ID NO:15." The Examiner erroneously concludes that "these improved results do not apply to the claims as ...broadly written." In addition, the Examiner alleges that "the prior art, when considered as a whole would have led one of skill in the art to the detection methods using probes comprising SEQ ID NO:15."

The Cited References Distinguished

The Examiner fails to satisfy the requirements to establish a *prima facie* case on multiple grounds. Specifically, 1) none of the cited references teach or suggest all the claim limitations; 2) the prior art combined with general knowledge in the art fails to include a suggestion or incentive to modify the references; and 3) the references fail to teach that the modification would reasonable chance of success.

Teach or Suggest Every Claim Limitation

The references separately, or in combination, fail to teach or suggest every limitation of the claims.

Claims 32-34 and 36 require contacting exposed RNA under hybridization conditions with oligonucleotide probes "capable of selectively hybridizing to said hypervariable regions" of a "raphidophyte cell." (Emphasis added). None of the cited references teach either a) that raphidophytes rRNA contains hypervariable regions, or b) the locations of raphidophyte rRNA hypervariable regions within raphidophyte RNA. Asai only discloses methods of amplifying general sequences of 18S rRNA, and is completely devoid of any disclosure of hypervariable regions. Lee only discloses the sequence of *H. akashiwo* rRNA, and does not teach the existence of, or specify the location of, hypervariable regions in the raphidophyte rRNA. Scholin et al. teach variable regions in an algae, but also fail to teach the location of rRNA hypervariable regions in raphidophytes.

Further, none of the references teach "identifying a hybridization complex to detect said raphidophyte cell," as required by claims 32-34 and 36. Asai teaches only detection of amplifying 18S RNA using FITC labeled primers, and applying a fluorescent polarization measurement to the resulting amplified product, not the hybridization complex of a probe and

rRNA. Neither Lee nor Scholin rectifies this deficiency of Asai. Lee fails to make any reference to a hybridization complex to detect a raphidophyte cell. Scholin also fails to teach a hybridization complex to detect a raphidophyte cell.

The references also fail to teach methods of detecting a raphidophyte cell using "a probe having a sequence comprising SEQ ID NO:15," as required by claim 36. Asai teaches only a method of amplifying 18S ribosomal RNA. Lee teaches only the inverse complement of SEQ ID NO:15, and does not provide any teaching for selecting a probe comprising SEQ ID NO:15. Neither Asai nor Scholin compensate for the deficiency of Lee, since neither Asai nor Scholin teach a hybridization probe comprising SEQ ID NO:15 or criteria for selecting a hybridization probe comprising SEQ ID NO:15.

Motivation or Suggestion to Combine

The references, separately or in combination, fail to provide the requisite motivation to combine their teachings to make the claimed invention. The prior art must provide a basis for the modification.

Ribosomal RNA sequences are structural sequences. To hybridize to a ribosomal RNA sequence, the target hypervariable region cannot involve a secondary or tertiary structure such as a self-hybridized region, and must be accessible to probes. To be detected in hybridization assays, the probes must be specific to a raphidophyte. In light of the structural nature of rRNA, none of the cited references provide the requisite motivation to alter the references.

First, none of the cited references provide the requisite motivation or suggestion to contact "the exposed RNA under hybridizing conditions with oligonucleotide probes capable of selectively hybridizing to hypervariable regions to form a hybridization complex." (Emphasis added). None of the references teach location of hypervariable regions in raphidophytes or how to select hybridization probes capable of hybridizing to hypervariable regions. As discussed above, Asai is devoid of any mention of hypervariable regions. Lee only teaches a partial sequence of *H. akashiwo* rRNA, but fails to teach which portion of the rRNA comprise hypervariable regions. Scholin teaches identifying variable regions of algae but fails to teach raphidophyte rRNA, which regions of raphidophyte rRNA are hypervariable, and how one of skill in the art would select probes capable of hybridizing to hypervariable regions.

Second, none of the references teach how to identify a probe-accessible hypervariable regions in raphidophytes. Designing probes to hybridize to a region of rRNA that forms a

secondary or tertiary structure would fail to hybridize to a hypervariable region. Asai, Lee, and Scholin all fail to indicate which raphidophyte rRNA regions are involved in structural interactions in the ribosome and are thus not accessible to probes using the hybridization method. Further, Asai, Lee, and Scholin all fail to teach hybridization to a hypervariable region of a raphidophyte, or how to identify hypervariable regions.

Regarding claim 36, it would not have been obvious for one of ordinary skill at the time the invention was made to use a sequence comprising SEQ ID NO:15 as a probe, as alleged by the Examiner. SEQ ID NO:15 hybridizes to a hypervariable region. As discussed above, hypervariable regions of rRNA are accessible to probes and are not involved in secondary and tertiary structural interactions in the ribosome. None of the references provide the requisite motivation or suggestion as to which raphidophyte sequences correspond to these regions. None of the references teaches or suggests which raphidophyte sequences are both accessible and not involved in structural interactions in the ribosome. Moreover, none of the references provide motivation to select the sequence comprising SEQ ID NO:15 as a probe for hypervariable regions.

The Examiner argues that it would have been obvious to modify the method of Asai so as to have detected *H. akashiwo* using sandwich hybridization or fluorescent *in situ* hybridization. The Examiner states that "the hybridization assay or fluorescent in situ hybridization assay of Scholin provides an equally effective means for detecting *H. akashiwo* and could have been performed rapidly using in an automated format." This reasoning, however, does not provide the requisite motivation to contact exposed RNA under hybridizing conditions with oligonucleotide probes capable of selectively hybridizing to hypervariable regions to form a hybridization complex," as required by the claims. As pointed out above, none of the cited references teach probes capable of selectively hybridizing to hypervariable regions of raphidophyte rRNA. Asai and Lee make no mention of hypervariable regions of raphidophytes. While Scholin teaches variable regions, Scholin also fails to teach anything about raphidophyte rRNA, or which regions of raphidophyte rRNA are hypervariable regions.

Reasonable Expectation of Success

The combined prior art teachings provide no reasonable expectation that the modification of Asai by Lee and Scholin would succeed.

As discussed above, ribosomal RNA sequences play a large structural role in the ribosome. To be detected in hybridization assays, the probes first must be specific to detected raphidophyte hypervariable regions, and second the detected regions must not form a secondary or tertiary structure by hybridizing to itself in other regions of the rRNA. To succeed in detecting a raphidophyte cell by the claimed methods, one of skill in the art would have to know the location of hypervariable regions, and the probes would have to be accessible to the hypervariable regions.

None of the cited references provide this guidance.

Asai only teaches amplification of a 18S rRNA in red tide plankton. The reference fails to disclose or even hint at the detection of hypervariable regions. Lee discloses only the sequence of rRNA, but like Asai fails to teach hypervariable regions of rRNA that are accessible to hybridization and not involved in ribosomal structural interactions. Scholin teaches ribosomal RNA of algae, but fails to teach one of skill in the art which regions of raphidophyte are hypervariable and how one skilled in the art would design probes capable of selectively hybridizing to hypervariable regions. Further, Scholin states at page 196 that "one must confirm that a positive reaction is specific for a target organism in question," and that the confirmation can be "accomplished by applying other methods, such as traditional microscopy, toxin analyses, molecular probes applied in a whole cell format." The lack of instruction on how to identify which regions are hypervariable, combined with requiring confirmation of the method, hardly provide one of skill in the art with a reasonable expectation of success in finding hypervariable regions in raphidophytes and using probes capable of hybridizing to those specific regions.

The difficulty in achieving success using the claimed methods is also apparent upon comparing the results discussed at pages 37-38 of the specification. As noted in Table 5, page 37, probes capable of hybridizing to different hypervariable regions result in vastly different binding efficiencies. For example, sandwich assays conducted using Het1.25aS (SEQ ID NO: 15) and Raphid1F (SEQ ID NO:8) result in significantly increased efficiency over all other assays, such as sandwich assays conducted using Het1.25bS (SEQ ID NO: 16) and Raphid2F (SEQ ID NO:9). One of skill in the art cannot merely take randomly chosen regions of ribosomal RNA and design probes capable of hybridizing to those sections. Instead, one of skill in the art must identify hypervariable regions of raphidophyte RNA, identify which

hypervariable regions are probe-accessible and are not involved in the secondary and tertiary role of ribosomal RNA.

Regarding claim 36, the references, taken as a whole, would not lead one of skill in the art to have a reasonable expectation of success in choosing a sandwich assay to detect raphidophytes using a probe having the sequence of SEQ ID NO:15. The complement of SEQ ID NO:15 is in a hypervariable region of *H. akaskiwo* rRNA. As discussed above, nothing in any of the references discloses selecting a hybridization region comprising SEQ ID NO:15. The Examiner alleges that "while ...the specification (page 36) teaches the improved results obtained when using probes consisting of SEQ ID NO:15, the claims are broadly drawn to probes comprising SEQ ID NO:15," and that "the improved results do not apply to the claims, as broadly written." The references, however, would not lead one of skill in the art to choose a sequence comprising SEQ ID NO:15. None of the references teach that SEQ ID NO: 15 IS A hypervariable region, or that hypervariable regions are accessible to probes.

Obvious to Try

Even assuming, *in arguendo*, that the references together had disclosed every aspect of the claimed invention, it would only be obvious to try to identify raphidophytes as claimed. Nothing in any of the references teaches what part of the sequence disclosed by Lee is a hypervariable region. Accordingly, one of skill in the art would not be able to design probes capable of hybridizing to a hypervariable region. From Scholin, one of skill in the art would only expect to succeed using algal probes for rRNA. One of skill in the art would be required to experiment with different raphidophytes probes to determine which raphidophyte rRNA regions are hypervariable, which regions of raphidophyte rRNA are accessible to probes, and which probes are capable of selectively hybridizing to hypervariable regions. None of the references provide any guidance to one of skill in the art to which raphidophyte regions are hypervariable regions and which are accessible to probes.

The disparity of success in trying to find probes capable of hybridizing to hypervariable regiosn is evident pages 37-38 of the specification, as discussed above. The difference between probes is evident upon consideration of data presented in Table 15. These data show the significant disparity in hybridization efficiencies using different probes. As pointed out above, one of skill in the art must identify hypervariable regions of raphidophyte RNA, identify which

hypervariable regions are probe-accessible, and identify which hypervariable regions are not involved in the secondary and tertiary role of ribosomal RNA.

These difficulties are underscored by Scholin et al. Scholin teach that "one must confirm that a positive reaction is specific for the target organism in question." (Emphasis added). In addition to a) identifying which regions of ribosomal rRNA are accessible to probes, b) identifying which regions are hypervariable, and c) which probes are capable of selectively hybridizing to the hypervariable regions, one of skill in the art would then have to identify whether the reaction was a positive one. One of skill in the art would thus be required to try several different probes corresponding to several different regions to succeed.

In view of the foregoing, the Examiner has failed to meet the requisite prima facie burden for obviousness. Applicant respectfully request that the rejection be withdrawn.

CONCLUSION

In light of the above amendments and remarks, Applicants believe that this case is now in condition for allowance. Should there be any remaining issues that remain unresolved, the Examiner is encouraged to telephone the undersigned.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 506812000120. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: April 2, 2003

By: Michael R. Ward
Registration No. (38,651)

Morrison & Foerster LLP
425 Market Street
San Francisco, California 94105-2482
Telephone: (415) 268-6237
Facsimile: (415) 268-7522